Access DB# 68353 (128)

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: RITA MITRA Examiner #: 77775 Date: 6/5/02
Art Unit: 1653 Phone Number 305-1211 Serial Number: 09/752,424
Mail Box and Bldg/Room Location: 1B01 CM1 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Treatment or prophylaxis of ischemic heart disease

Inventors (please provide full names): MASAFUMI KITAKAZE

Earliest Priority Filing Date: 3/31/2000

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

I request an expedited literature search (Patent and Non Patent) because this application is a date case.

The search should encompass a pharmaceutical composition for use in treatment or prophylaxis of ischemic heart disease, herein the composition [illegible] active ingredient which can increase [illegible] intracellular cGMP production by acting on a natriuretic peptide receptor.

Keywords:
infarct organ
infarction
cGMP
natriuretic
ischemic disease

Point of Contact:
Barb O'Bryen
Technical Information Specialist
STIC CM1 6A05 308-4291

****

STAFF USE ONLY		Type of Search		Vendors and cost where applicable	
Searcher:		NA Sequence (#)		STN	
Searcher Phone #:		AA Sequence (#)		Dialog	
Searcher Location:		Structure (#)		Questel/Orbit	
Date Searcher Picked Up:		Bibliographic	✓	Dr.Link	
Date Completed:		Litigation		Lexis/Nexis	
Searcher Prep & Review Time:	30	Fulltext		Sequence Systems	
Clerical Prep Time:		Patent Family		WWW/Internet	
Online Time:		Other		Other (specify)	

PTO-1590 (1-2000)

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=> fil reg; d rn cn
FILE 'REGISTRY' ENTERED AT 11:28:58 ON 07 JUN 2002
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STRUCTURE FILE UPDATES:    5 JUN 2002  HIGHEST RN 426206-38-4
DICTIONARY FILE UPDATES:   5 JUN 2002  HIGHEST RN 426206-38-4

TSCA INFORMATION NOW CURRENT THROUGH January 7, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf


L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   7665-99-8  REGISTRY
CN   Guanosine, cyclic 3',5'-(hydrogen phosphate) (8CI, 9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   4H-Furo[3,2-d]-1,3,2-dioxaphosphorin, guanosine deriv.
CN   Guanosine 3',5'-phosphate (cyclic) (7CI)
OTHER NAMES:
CN   3',5'-Cyclic GMP
CN   3',5'-GMP
CN   cGMP
CN   Cyclic 3',5'-GMP
CN   Cyclic 3',5'-guanylic acid
CN   Cyclic GMP
CN   Cyclic guanosine 3',5'-monophosphate
CN   Cyclic guanosine monophosphate
CN   Guanosine 3',5'-monophosphate
CN   Guanosine 3',5'-phosphate
CN   Guanosine cyclic 3',5'-monophosphate
CN   Guanosine cyclic 3',5'-phosphate
```

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=> fil capl; d que l10
FILE 'CAPLUS' ENTERED AT 12:21:04 ON 07 JUN 2002
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FILE COVERS 1907 - 7 Jun 2002  VOL 136 ISS 23
FILE LAST UPDATED: 5 Jun 2002  (20020605/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.


L1             1 SEA FILE=REGISTRY ABB=ON  "CYCLIC GMP"/CN
L2         15579 SEA FILE=CAPLUS ABB=ON  L1 OR (CYCLIC(2A)(GMP OR GUANOSINE(2A)?
                 PHOSPHATE))/OBI OR CGMP/OBI
L3         24388 SEA FILE=CAPLUS ABB=ON  HEART/CW(L)(INFARC? OR ISCHEM? OR
                 ISCHAEM?)
L4          2134 SEA FILE=CAPLUS ABB=ON  ANTI-ISCHEMIC AGENTS/CT
L7          9915 SEA FILE=CAPLUS ABB=ON  NATRIURETIC/OBI
L10           11 SEA FILE=CAPLUS ABB=ON  (L3 OR L4) AND L7 AND L2


=> fil medl;d que l20; d que l27

FILE 'MEDLINE' ENTERED AT 12:21:05 ON 07 JUN 2002

 FILE LAST UPDATED: 6 JUN 2002 (20020606/UP).  FILE COVERS 1958 TO DATE.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.


L11 .      14003 SEA FILE=MEDLINE ABB=ON  CYCLIC GMP+NT/CT
L12       199997 SEA FILE=MEDLINE ABB=ON  MYOCARDIAL ISCHEMIA+NT/CT
L13         4967 SEA FILE=MEDLINE ABB=ON  MYOCARDIAL REPERFUSION INJURY/CT
L14        11044 SEA FILE=MEDLINE ABB=ON  ATRIAL NATRIURETIC FACTOR/CT
L15          407 SEA FILE=MEDLINE ABB=ON  NATRIURETIC HORMONE/CT
L16         1142 SEA FILE=MEDLINE ABB=ON  NATRIURETIC PEPTIDE, BRAIN/CT
L19         6466 SEA FILE=MEDLINE ABB=ON  L11(L)ME/CT - Subheading ME = metabolism
L20            7 SEA FILE=MEDLINE ABB=ON  L19 AND (L12 OR L13) AND (L14 OR L15
                 OR L16)



L11        14003 SEA FILE=MEDLINE ABB=ON  CYCLIC GMP+NT/CT
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L12      199997 SEA FILE=MEDLINE ABB=ON  MYOCARDIAL ISCHEMIA+NT/CT
L13        4967 SEA FILE=MEDLINE ABB=ON  MYOCARDIAL REPERFUSION INJURY/CT
L26        1196 SEA FILE=MEDLINE ABB=ON  RECEPTORS, ATRIAL NATRIURETIC
                FACTOR/CT
L27           0 SEA FILE=MEDLINE ABB=ON  L11 AND L26 AND (L12 OR L13)


=> fil embase; d que l42; d que l47; s l42 or l47

FILE 'EMBASE' ENTERED AT 12:21:06 ON 07 JUN 2002
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 FILE COVERS 1974 TO 6 Jun 2002 (20020606/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L28        28988 SEA FILE=EMBASE ABB=ON  HEART MUSCLE ISCHEMIA/CT
L29        74379 SEA FILE=EMBASE ABB=ON  HEART INFARCTION+NT/CT
L30          281 SEA FILE=EMBASE ABB=ON  HEART INFARCTION LOCALIZATION/CT
L31          879 SEA FILE=EMBASE ABB=ON  HEART INFARCTION PREVENTION/CT
L32           18 SEA FILE=EMBASE ABB=ON  HEART INFARCTION REHABILITATION/CT
L33         3667 SEA FILE=EMBASE ABB=ON  HEART INFARCTION SIZE/CT
L34        12619 SEA FILE=EMBASE ABB=ON  CYCLIC GMP/CT
L36            3 SEA FILE=EMBASE ABB=ON  NATRIURETIC FACTOR RECEPTOR/CT
L37          642 SEA FILE=EMBASE ABB=ON  ATRIAL NATRIURETIC FACTOR RECEPTOR/CT
L41         8190 SEA FILE=EMBASE ABB=ON  REPERFUSION INJURY/CT
L42            6 SEA FILE=EMBASE ABB=ON  ((L28 OR L29 OR L30 OR L31 OR L32 OR
                L33) OR L41) AND L34 AND (L36 OR L37)



L28        28988 SEA FILE=EMBASE ABB=ON  HEART MUSCLE ISCHEMIA/CT
L29        74379 SEA FILE=EMBASE ABB=ON  HEART INFARCTION+NT/CT
L30          281 SEA FILE=EMBASE ABB=ON  HEART INFARCTION LOCALIZATION/CT
L31          879 SEA FILE=EMBASE ABB=ON  HEART INFARCTION PREVENTION/CT
L32           18 SEA FILE=EMBASE ABB=ON  HEART INFARCTION REHABILITATION/CT
L33         3667 SEA FILE=EMBASE ABB=ON  HEART INFARCTION SIZE/CT
L34        12619 SEA FILE=EMBASE ABB=ON  CYCLIC GMP/CT
L35        13312 SEA FILE=EMBASE ABB=ON  NATRIURETIC FACTOR+NT/CT
L41         8190 SEA FILE=EMBASE ABB=ON  REPERFUSION INJURY/CT
L45           32 SEA FILE=EMBASE ABB=ON  ((L28 OR L29 OR L30 OR L31 OR L32 OR
                L33) OR L41) AND L34 AND (L35)
L46         2472 SEA FILE=EMBASE ABB=ON  L35(L)(PD OR AD OR PK OR DT)/CT
L47           11 SEA FILE=EMBASE ABB=ON  L46 AND L45
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Subheadings
PD - pharmacology
AD - administration & dosage
PK - pharmacokinetics
DT - drug therapy

```
L69           13 L42 OR L47

=> fil wpids; d que l54; d que l57; s l54 or l57

FILE 'WPIDS' ENTERED AT 12:21:07 ON 07 JUN 2002
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FILE LAST UPDATED: 03 JUN 2002              <20020603/UP>
MOST RECENT DERWENT UPDATE          200235   <200235/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> The BATCH option for structure searches has been
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enabled in WPINDEX/WPIDS and WPIX >>>

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY >>>

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

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GUIDES, PLEASE VISIT:
http://www.derwent.com/userguides/dwpi_guide.html <<<

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L48          579 SEA FILE=WPIDS ABB=ON  NATRIURETIC
L49          475 SEA FILE=WPIDS ABB=ON  CYCLIC(2A)(GMP OR (GUANOSINE(2A)?PHOSPHA
                 TE?)) OR CGMP
L50         9750 SEA FILE=WPIDS ABB=ON  (MYOCARDI? OR CARDI? OR HEART)(5A)(INFAR
                 CT? OR ISCHEM? OR ISCHAEM?)
L51         1639 SEA FILE=WPIDS ABB=ON  REPERFUSION(3A)INJUR?
L53        31314 SEA FILE=WPIDS ABB=ON  RECEPTOR#
L54            2 SEA FILE=WPIDS ABB=ON  L48 AND L49 AND (L50 OR L51) AND L53



L48          579 SEA FILE=WPIDS ABB=ON  NATRIURETIC
L49          475 SEA FILE=WPIDS ABB=ON  CYCLIC(2A)(GMP OR (GUANOSINE(2A)?PHOSPHA
                 TE?)) OR CGMP
L50         9750 SEA FILE=WPIDS ABB=ON  (MYOCARDI? OR CARDI? OR HEART)(5A)(INFAR
                 CT? OR ISCHEM? OR ISCHAEM?)
L51         1639 SEA FILE=WPIDS ABB=ON  REPERFUSION(3A)INJUR?
L57            2 SEA FILE=WPIDS ABB=ON  L48 (15A) L49 (15A) (L50 OR L51)



L70            3 L54 OR L57

=> fil drugu; d que l66; d que l64; s l66 or l64

FILE 'DRUGU' ENTERED AT 12:21:08 ON 07 JUN 2002
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FILE LAST UPDATED: 06 JUN 2002      <20020606/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  SDI'S MAY BE RUN WEEKLY OR MONTHLY AS OF JUNE 2001.  <<<
>>>  (WEEKLY IS THE DEFAULT). FOR PRICING INFORMATION     <<<
>>>  SEE HELP COST                                        <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<



L58         2705 SEA FILE=DRUGU ABB=ON  CGMP/CT OR CYCLIC-GMP/CT OR CYCLIC
                 -GMP/CT
L59         4876 SEA FILE=DRUGU ABB=ON  NATRIURETIC
L60        25392 SEA FILE=DRUGU ABB=ON  (MYOCARDI? OR CARDI? OR HEART)(5A)(INFAR
                 CT? OR ISCHEM? OR ISCHAEM?)
L61         2147 SEA FILE=DRUGU ABB=ON  REPERFUSION(3A)INJUR?
L63        24332 SEA FILE=DRUGU ABB=ON  MYOCARD.INFARCT/CT OR MYOCARD.INFARCT./C
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              T
L65       106917 SEA FILE=DRUGU ABB=ON  RECEPTOR#
L66            1 SEA FILE=DRUGU ABB=ON  L58 AND L59 AND (L60 OR L61 OR L63) AND
                 L65



L58         2705 SEA FILE=DRUGU ABB=ON  CGMP/CT OR CYCLIC-GMP/CT OR CYCLIC
                 -GMP/CT
L59         4876 SEA FILE=DRUGU ABB=ON  NATRIURETIC
L60        25392 SEA FILE=DRUGU ABB=ON  (MYOCARDI? OR CARDI? OR HEART)(5A)(INFAR
                 CT? OR ISCHEM? OR ISCHAEM?)
L61         2147 SEA FILE=DRUGU ABB=ON  REPERFUSION(3A)INJUR?
L63        24332 SEA FILE=DRUGU ABB=ON  MYOCARD.INFARCT/CT OR MYOCARD.INFARCT./C
                 T
L64           13 SEA FILE=DRUGU ABB=ON  L58 AND L59 AND (L60 OR L61 OR L63)



L71           13 L66 OR L64

=> dup rem 120,171,110,169,170
FILE 'MEDLINE' ENTERED AT 12:21:42 ON 07 JUN 2002

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PROCESSING COMPLETED FOR L20
PROCESSING COMPLETED FOR L71
PROCESSING COMPLETED FOR L10
PROCESSING COMPLETED FOR L69
PROCESSING COMPLETED FOR L70
L72            38 DUP REM L20 L71 L10 L69 L70 (9 DUPLICATES REMOVED)
                  ANSWERS '1-7' FROM FILE MEDLINE
                  ANSWERS '8-19' FROM FILE DRUGU
                  ANSWERS '20-27' FROM FILE CAPLUS
                  ANSWERS '28-35' FROM FILE EMBASE
                  ANSWERS '36-38' FROM FILE WPIDS

=> d ibib ab hitrn l72 1-38; fil hom

L72  ANSWER 1 OF 38     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:    2001429319     MEDLINE
DOCUMENT NUMBER:     21369524   PubMed ID: 11476750
TITLE:               Intravenous administration of the natriuretic peptide
                     urodilatin at low doses during coronary reperfusion limits
                     infarct size in anesthetized pigs.
AUTHOR:              Padilla F; Garcia-Dorado D; Agullo L; Barrabes J A; Inserte
                     J; Escalona N; Meyer M; Mirabet M; Pina P; Soler-Soler J
CORPORATE SOURCE:    Department of Cardiology, Hospital General Universitari
                     Vall d'Hebron, Pg. Vall d'Hebron 119-129, 08035, Barcelona,
                     Spain.
SOURCE:              CARDIOVASCULAR RESEARCH, (2001 Aug 15) 51 (3) 592-600.
```

Journal code: COR; 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20011008
Entered Medline: 20011004

AB OBJECTIVE: It has been shown that cGMP content is reduced in post-ischemic myocardium, and that stimulation of cGMP synthesis prevents cardiomyocyte hypercontracture and cell death in vitro. This study was aimed at determining whether administration of the natriuretic peptide urodilatin (URO) at the time of reperfusion could limit myocardial cell death secondary to transient coronary occlusion. METHODS: The relation between cGMP content in reperfused myocardium and the extent of cell death was investigated in isolated rat hearts (n=62) receiving different URO concentrations during initial reperfusion. The dose of intravenous URO necessary to obtain the targeted increase in cGMP in reperfused myocardium was investigated in ten pigs submitted to transient coronary occlusion (CO), and the effect of two selected doses of URO on infarct size was investigated in 22 pigs. RESULTS: cGMP was severely reduced in post-ischemic rat hearts. Addition of 0.01 microM URO during the first 15 min of reperfusion had no effect on myocardial cGMP content, functional recovery or LDH release in hearts submitted to 40 or 60 min of ischemia. At 0.05 microM, URO increased myocardial cGMP to 111% of values in normoxic hearts, improved functional recovery (P=0.01) and reduced peak LDH released by 40% (P=0.02). The beneficial effect of urodilatin was abolished by ANP receptor inhibition. At 1 microM, URO increased cGMP in reperfused myocardium to 363% of normoxic controls and had no beneficial effect. In pigs allocated to 47 min of CO and 5 min of reperfusion, cGMP was markedly reduced in reperfused myocardium. Intravenous URO at 10 ng/kg per min during the first 25 min of reperfusion normalized myocardial cGMP after 5 min of reflow (95% of control myocardium), and reduced infarct size by 40% (P=0.04). At 50 ng/kg per min, urodilatin increased myocardial cGMP in reperfused myocardium to 335% of control myocardium and failed to significantly reduce infarct size (46 vs. 66%, P=0.125). None of these doses had detectable hemodynamic effects. CONCLUSIONS: Intravenous low-dose URO at the time of reperfusion normalizes myocardial cGMP and limits necrosis. Large doses of URO increasing myocardial cGMP well over normal values may lack this beneficial effect.

L72 ANSWER 2 OF 38 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000192599 MEDLINE
DOCUMENT NUMBER: 20192599 PubMed ID: 10728355
TITLE: Urodilatin limits acute reperfusion injury in the isolated rat heart.
AUTHOR: Inserte J; Garcia-Dorado D; Agullo L; Paniagua A; Soler-Soler J
CORPORATE SOURCE: Servicio de Cardiologia, Hospital General Universitari Vall d'Hebron, Barcelona, Spain.
SOURCE: CARDIOVASCULAR RESEARCH, (2000 Jan 14) 45 (2) 351-9.
Journal code: COR; 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000421
Last Updated on STN: 20000421
Entered Medline: 20000411

AB OBJECTIVES: Hypercontracture is an important mechanism of myocyte death during reperfusion. cGMP modulates the sensitivity of contractile

myofilaments to Ca2+, and increasing cGMP concentration during the last minutes of anoxia prevents reoxygenation-induced hypercontracture in isolated cardiomyocytes. The purpose of this study was to determine whether stimulation of particulate guanylyl cyclase with the natriuretic peptide urodilatin, given at the time of reperfusion, reduces myocardial necrosis in the rat heart submitted to transient ischemia. METHODS: Isolated rat hearts (n = 38) were submitted to either 40 or 60 min of no-flow ischemia and 2 h of reperfusion, and were allocated to receive or not receive 0.05 microM urodilatin during the first 15 min of reperfusion or non-reperfusion treatment. RESULTS: A marked reduction in myocardial cGMP concentration was observed in control hearts during reperfusion after 40 or 60 min of ischemia. Urodilatin significantly attenuated cGMP depletion during initial reperfusion, markedly improved contractile recovery after 40 min of ischemia ($P < 0.0309$), and reduced reperfusion-induced increase in left ventricular end-diastolic pressure ($P = 0.0139$), LDH release ($P = 0.0263$), and contraction band necrosis ($P = 0.0179$) after 60 min of ischemia. The beneficial effect of urodilatin was reproduced by the membrane permeable cGMP analog 8-Bromo-cGMP. CONCLUSIONS: These results indicate that reduced cGMP concentration may impair myocyte survival during reperfusion. Stimulation of particulate guanylyl cyclase may appear as a new strategy to prevent immediate lethal reperfusion injury.

L72 ANSWER 3 OF 38 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 96388715 MEDLINE
DOCUMENT NUMBER: 96388715 PubMed ID: 8796115
TITLE: The beneficial effects of atrial natriuretic peptide on arrhythmias and myocardial high-energy phosphates after reperfusion.
AUTHOR: Takata Y; Hirayama Y; Kiyomi S; Ogawa T; Iga K; Ishii T; Nagai Y; Ibukiyama C
CORPORATE SOURCE: Second Department of Internal Medicine, Tokyo Medical College, Japan.
SOURCE: CARDIOVASCULAR RESEARCH, (1996 Aug) 32 (2) 286-93.
Journal code: COR; 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19990129
Entered Medline: 19970128

AB OBJECTIVES: The aim of this investigation was to test whether the administration of atrial natriuretic peptide (ANP) has cardioprotective effects against ischaemic and reperfusion injury. METHODS: Thoracotomized dogs underwent a 30 min left circumflex coronary artery occlusion and 60 min of reperfusion (control group; n = 16). The ANP group (n = 9) received a 20 micrograms bolus injection of synthetic alpha human ANP (SUN 4936) followed by infusion at a dose of 0.1 microgram/kg/min from the beginning of coronary occlusion to the end of the procedure. RESULTS: Administration of exogenous ANP increased plasma ANP immediately and maintained levels at 3000 pg/ml, resulting in an 8-fold increase in plasma cyclic guanosine monophosphate (cGMP) levels. Plasma ANP and plasma cGMP levels did not change at all in controls. There were no significant differences in haemodynamic parameters during ischaemia and reperfusion between the groups. In the ANP group, the prevalence and frequency of ventricular extrasystoles within 10 min after reperfusion decreased markedly [ANP 22% vs. control 100%, $P < 0.01$, and ANP 1 (1) vs. control 92 (50), $P < 0.05$, respectively]. No dog in the ANP group had ventricular fibrillation (VF), but the incidence of VF was not statistically significant between the groups [ANP 0% vs. control 25%]. ATP content in the inner layers of the ischaemic myocardium in the ANP group was higher than in controls ($P <$

0.05) [1.92 (0.28) vs. 1.18 (0.13) mumol/g wet weight]. There was no significant difference in the content of myocardial tissue angiotensin II between the groups. CONCLUSIONS: These data show that the infusion of ANP has cardioprotective effects on myocardial ischaemia and reperfusion in this model. These beneficial effects are probably due to direct effects through cGMP rather than haemodynamic changes.

L72 ANSWER 4 OF 38 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 93374007 MEDLINE
DOCUMENT NUMBER: 93374007 PubMed ID: 8396039
TITLE: Atrial natriuretic factor influences in vivo plasma, lung and aortic wall cGMP concentrations differently.
AUTHOR: Arnal J F; el Amrani A I; Michel J B
CORPORATE SOURCE: Unit 367 INSERM, Paris, France.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1993 Jun 24) 237 (2-3) 265-73.
Journal code: EN6; 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931022
Last Updated on STN: 19970203
Entered Medline: 19931004

AB Atrial natriuretic factor (ANF) promotes natriuresis and diuresis, increases vascular permeability and may induce peripheral vasodilatation. Endothelium-derived relaxing factor (EDRF), which is nitric oxide (NO), promotes local vasodilatation. ANF and EDRF-NO both cause vascular relaxation by generating cGMP via the activation of the particulate and soluble guanylate cyclases, respectively. This study examines the in vivo effect of exogenous ANF administration in normal Wistar rats, and of increased endogenous ANF in an experimental model of heart failure, on plasma and tissue cGMP concentrations. Low-dose ANF increased plasma and pulmonary cGMP concentrations, whereas 10-fold higher doses were necessary to increase aorta cGMP concentrations. Rats with a myocardial infarction had increased plasma ANF and cGMP and pulmonary cGMP concentrations, but aorta cGMP concentration remained similar to that of sham-operated rats. NG nitro L-arginine methyl ester (L-NAME) was administered chronically to sham-operated and myocardial infarction rats to block NO-synthase: soluble guanylate cyclase activity. L-NAME did not lower the increase in plasma ANF concentration or in urinary, plasma or pulmonary cGMP concentration. In contrast, L-NAME reduced the aorta cGMP concentration 6-fold, despite an increased level of circulating ANF. In summary, the pathophysiological range of plasma ANF concentrations greatly increases plasma and pulmonary cGMP concentrations (by activating particulate guanylate cyclase), but has little influence on the aorta cGMP concentration (which remains mainly dependent on NO-synthase: soluble guanylate cyclase activity).

L72 ANSWER 5 OF 38 MEDLINE
ACCESSION NUMBER: 2001530146 MEDLINE
DOCUMENT NUMBER: 21460402 PubMed ID: 11577026
TITLE: Mechanisms of L-type Ca(2+) current downregulation in rat atrial myocytes during heart failure.
AUTHOR: Boixel C; Gonzalez W; Louedec L; Hatem S N
CORPORATE SOURCE: INSERM Unite 460, Faculte de Medecine Xavier Bichat, Paris, France.
SOURCE: CIRCULATION RESEARCH, (2001 Sep 28) 89 (7) 607-13.
Journal code: DAJ; 0047103. ISSN: 1524-4571.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20011029
Entered Medline: 20011025

AB Downregulation of the L-type Ca(2+) current (I(Ca)) is an important determinant of the electrical remodeling of diseased atria. Using a rat model of heart failure (HF) due to ischemic cardiopathy, we studied I(Ca) in isolated left atrial myocytes with the whole-cell patch-clamp technique and biochemical assays. I(Ca) density was markedly reduced (1.7+/-0.1 pA/pF) compared with sham-operated rats (S) (4.1+/-0.2 pA/pF), but its gating properties were unchanged. Calcium channel alpha(1C)-subunit quantities were not significantly different between S and HF. The beta-adrenergic agonist isoproterenol (1 micromol/L) had far greater stimulatory effects on I(Ca) in HF than in S (2.5- versus 1-fold), thereby suppressing the difference in current density. Dialyzing cells with 100 micromol/L cAMP or pretreating them with the phosphatase inhibitor okadaic acid also increased I(Ca) and suppressed the difference in density between S and HF. Intracellular cAMP content was reduced more in HF than in S. The phosphodiesterase inhibitor 3-isobutyl-1-methyl-xanthine had a greater effect on I(Ca) in HF than in S (76.0+/-11.2% versus 15.8+/-21.2%), whereas the inhibitory effect of atrial natriuretic peptide on I(Ca) was more important in S than in HF (54.1+/-4.8% versus 24.3+/-8.8%). Cyclic GMP extruded from HF myocytes was enhanced compared with S (55.8+/-8.0 versus 6.2+/-4.0 pmol. mL(-1)). Thus, I(Ca) downregulation in atrial myocytes from rats with heart failure is caused by changes in basal cAMP-dependent regulation of the current and is associated with increased response to catecholamines.

L72 ANSWER 6 OF 38 MEDLINE
ACCESSION NUMBER: 1998309284 MEDLINE
DOCUMENT NUMBER: 98309284 PubMed ID: 9647069
TITLE: Atrial natriuretic peptide-induced release of cyclic guanosine monophosphate by coronary bypass grafts.
AUTHOR: Bonatti J; Dichtl W; Dworzak E A; Antretter H; Unger F; Puschendorf B; Dapunt O E
CORPORATE SOURCE: Division of Cardiac Surgery, University Clinic of Surgery, Innsbruck, Austria.. johannes.o.bonatti@uibk.ac.at
SOURCE: ANNALS OF THORACIC SURGERY, (1998 Jun) 65 (6) 1621-4.
Journal code: 683; 15030100R. ISSN: 0003-4975.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980723
Last Updated on STN: 19980723
Entered Medline: 19980716

AB BACKGROUND: Superior long-term patency rates of the internal mammary artery (IMA) versus saphenous vein (SV) after coronary artery bypass grafting are well documented. Higher production rates of vasodilating and platelet-inhibiting mediators (prostacyclin and nitric oxide) by the IMA seem to have a major impact on its long-term durability and resistance to coronary artery graft disease. For the right gastroepiploic artery (RGEA) marked release of protective mediators is reported as well. The vasodilating effect of cyclic guanosine monophosphate (cGMP) released after stimulation by atrial natriuretic peptide might serve as another graft protective system. The aim of the present study was to determine cGMP release by IMA, RGEA, and SV after atrial natriuretic peptide challenge. METHODS: Samples of human IMA (n = 19), RGEA (n = 7), and SV (n = 18) discarded during coronary artery bypass grafting were stimulated with 10(-6) mol/L atrial natriuretic peptide after a resting phase in nutrient medium. Release of cGMP was determined by 125-iodide radioimmunoassay. RESULTS: Basal cGMP production rates of the IMA (759.9

+/- 277.0 fmol/cm2) and RGEA (739.9 +/- 186.0 fmol/cm2) were higher than production rates of SV (281.2 +/- 64.0 fmol/cm2). Application of atrial natriuretic peptide led to a statistically significant increase of cGMP release in IMA grafts (1,939.3 +/- 778.0 fmol/cm2), whereas RGEA (618.4 +/- 141.3 fmol/cm2) and SV (221.7 +/- 64.5 fmol/cm2) remained at basal levels ($p < 0.05$). CONCLUSIONS: From these data we conclude that the IMA in comparison with the RGEA and SV produces more extracellular cGMP when stimulated by atrial natriuretic peptide. This effect might support the cGMP-mediated protective properties of nitric oxide and could underline the extraordinary suitability of the IMA as a bypass conduit.

L72 ANSWER 7 OF 38 MEDLINE
ACCESSION NUMBER: 94036967 MEDLINE
DOCUMENT NUMBER: 94036967 PubMed ID: 8221770
TITLE: Discrepancy between plasma and aortic wall cyclic guanosine monophosphate in an experimental model of congestive heart failure.
AUTHOR: Arnal J F; Hofmann F; Michel J B
CORPORATE SOURCE: Unit 367 INSERM, Paris, France.
SOURCE: CARDIOVASCULAR RESEARCH, (1993 Jun) 27 (6) 1094-100.
Journal code: COR; 0077427. ISSN: 0008-6363.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19940117
Entered Medline: 19931202

AB OBJECTIVES: The state of the vasodilator systems in congestive heart failure is poorly defined. Plasma atrial natriuretic peptide is increased, whereas endothelium derived relaxing factor activity can be decreased. Atrial natriuretic peptide and endothelium derived relaxing factor both cause vascular relaxation by generating cyclic guanosine monophosphate (cGMP), by activating the particulate and the soluble guanylate cyclase, respectively. This study examines the biological effects of atrial natriuretic peptide and endothelium derived relaxing factor in experimental heart failure by assessing the plasma, urinary, and tissue concentrations of their common second messenger cGMP. METHODS: Myocardial infarctions ($n = 31$) were induced and sham operations ($n = 25$) were performed on Wistar rats, and the rats were monitored for three months. Aortic and pulmonary cGMP contents were measured, as the aorta is mainly matrix and smooth muscle cells, and the lung is particularly rich in capillaries, hence in endothelial cells. The concentrations of the other second messenger cyclic adenosine monophosphate (cAMP) was also determined, as were those of cGMP dependent protein kinase in the arteries. RESULTS: 17 of the 31 rats with myocardial infarction had oedema. The total heart weight to body weight ratio and the ratio of the myocardium haemodynamically upstream from the infarcted left ventricle to body weight were increased in proportion to the infarct size. Plasma atrial natriuretic peptide and plasma and urinary cGMP concentrations were increased in proportion to the degree of heart failure ($p < 0.0001$). The pulmonary cGMP concentration was significantly higher in the rats with myocardial infarction than in the control group ($p < 0.0001$). Pulmonary cGMP concentrations were correlated with the plasma concentrations of atrial natriuretic peptide and cGMP ($r2 = 0.59$ and 0.66 respectively, $p < 0.0001$). The cGMP, cAMP, and cGMP, and cGMP dependent kinase concentrations in the aortic wall of rats with myocardial infarctions were the same as in control rats. CONCLUSIONS: The increase in plasma, urinary, and pulmonary cGMP in rats with myocardial infarctions were highly correlated with the increase in circulating atrial natriuretic peptide. By contrast, the aortic cGMP concentration was unchanged in these rats, despite high plasma atrial natriuretic peptide. In congestive heart

failure, a discrepancy seems to exist between pulmonary (mainly endothelium) and aortic wall (mainly smooth muscle cells) cGMP.

L72 ANSWER 8 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENTDUPLICATE 2
ACCESSION NUMBER: 2001-36136 DRUGU P
TITLE: Blockade of the **natriuretic** peptide **receptor** guanylyl cyclase-A inhibits NF-kappa-B activation and alleviates **myocardial ischemia/reperfusion injury**.
AUTHOR: Izumi T; Saito Y; Kishimoto I; Harada M; Kuwahara K; Hamanaka I; Takahashi N; Kawakami R; Li Y; Takemura G
CORPORATE SOURCE: Univ.Kyoto; Univ.Gifu; Univ.Texas-Southwestern; Univ.Jikei
LOCATION: Kyoto, Gifu; Tokyo, Jap.; Dallas, Tex., USA
SOURCE: J.Clin.Invest. (108, No. 2, 203-13, 2001) 7 Fig. 1 Tab. 56 Ref.
CODEN: JCINAO ISSN: 0021-9738
AVAIL. OF DOC.: Dept Medicine and Clinical Science, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8397, Japan. (Y.S.). (e-mail: yssaito@kuhp.kyoto-u.ac.jp).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The effect of the guanylyl cyclase A antagonist HS-142-1 (Kyowa-Hakko) on **myocardial infarct** size was studied in mice subjected to **myocardial ischemia**/reperfusion. Pretreatment with i.v. HS-142-1 decreased infarct size and prevented P-selectin induction in coronary endothelial cells. The results suggest that inhibition of guanylyl cyclase A may be a useful way of treating **reperfusion injury**.

L72 ANSWER 9 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-27002 DRUGU T E
TITLE: Intravenous atrial **natriuretic** peptide prevents left ventricular remodeling in patients with first anterior acute **myocardial infarction**.
AUTHOR: Hayashi M; Tsutamoto T; Wada A; Maeda K; Mabuchi N; Tsutsui T; Horie H; Ohnishi M; Kinoshita M
CORPORATE SOURCE: Univ.Shiga
LOCATION: Otsu, Jap.
SOURCE: J.Am.Coll.Cardiol. (37, No. 7, 1820-26, 2001) 2 Fig. 4 Tab. 31 Ref.
CODEN: JACCDI ISSN: 0735-1097
AVAIL. OF DOC.: First Department of Internal Medicine, Shiga University of Medical Science, Tsukinowa, Seta, Otsu 520-2192, Japan. (T.T.). (e-mail: tutamoto@belle.shiga-med.ac.jp).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB I.v. atrial **natriuretic** peptide (ANP, atrial-**natriuretic**-factor) infusion, and to a lesser extent, nitroglycerin (GTN, nitroglycerol), administered immediately after direct PTCA, increased the LV ejection fraction in a prospective, randomized study of 60 patients with a 1st anterior acute MI. ANP, but not GTN, prevented the increase in LV end-diastolic volume index. The LV end-systolic volume index was reduced by ANP but was slightly increased by GTN. ANP, but not GTN, was associated with increased plasma levels of ANP and cGMP. ANP also suppressed the plasma aldosterone level, angiotensin II, and endothelin-1. Results show that treatment with an ANP infusion started immediately after direct PTCA can prevent LV dilation and improve LV ejection fraction in patients with a 1st anterior acute

MI.

L72 ANSWER 10 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1996-41526 DRUGU P E
TITLE: Inhibition of both angiotensin-converting enzyme and neutral endopeptidase by S21402 (RB105) in rats with experimental **myocardial infarction.**
AUTHOR: Gonzalez W; Beslot F; Laboulandine I; Fournie Zaluski M C; Roques B P; Michel J B
CORPORATE SOURCE: INSERM
LOCATION: Paris, Fr.
SOURCE: J.Pharmacol.Exp.Ther. (278, No. 2, 573-81, 1996) 8 Fig. 2 Tab. 55 Ref.
CODEN: JPETAB ISSN: 0022-3565
AVAIL. OF DOC.: Department of Pharmacology, College of Medicine, Given Building, Burlington, VT 05405-0068, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB I.v. infusion of RB-105 (S-21402) lowered the MAP and restored natriuresis in MI rats irrespective of the degree of MI. RB-105 further increased the already elevated PRA but had no effect on the plasma atrial **natriuretic** factor (ANF) level in MI rats. However, RB-105 increased not only the plasma cGMP level but also the urinary output of ANF, cGMP and bradykinin (BK) in MI rats, all these responses being proportional to infarct size. These findings indicate that this dual inhibitor of ACE and neutral endopeptidase (RB-105) may represent a promising therapeutic option in CHF since it offers a combination of vasodilator and **natriuretic** actions.

L72 ANSWER 11 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1995-48566 DRUGU P B
TITLE: Effect of nifedipine on cyclic GMP turnover in cultured coronary smooth muscle cells.
AUTHOR: Kishi Y; Watanabe T; Makita T; Sakita S; Watanabe R; Ashikaga T; Numano F
CORPORATE SOURCE: Univ.Tokyo
LOCATION: Tokyo, Jap.
SOURCE: J.Cardiovasc.Pharmacol. (26, No. 4, 590-95, 1995) 5 Fig. 1 Tab. 34 Ref.
CODEN: JCPCDT ISSN: 0160-2446
AVAIL. OF DOC.: Third Department of Medicine, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113, Japan.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB In cultured porcine coronary smooth muscle cells, nifedipine (Bayer) slightly decreased basal guanylate cyclase activity, inhibited cGMP hydrolysis by direct inhibition of calmodulin-stimulated isoform of phosphodiesterase (type I PDE), and enhanced sodium nitroprusside (SNP, Sigma-Chem.)-induced cGMP accumulation. BAY-K-8644 (Bayer) had no effect on enhancement of SNP-evoked cGMP accumulation by nifedipine.Nicardipine HCl (Yamanouchi) and nisoldipine (Bayer) also inhibited type I PDE. Diltiazem HCl (Tanabe) and verapamil HCl (Eisai) had little effect on cGMP hydrolysis or SNP-evoked cGMP accumulation. The inhibitory effect of nifedipine on cGMP hydrolysis may contribute to its coronary vasodilating effect and prevention of coronary spasm in patients with **ischemic heart** disease.

L72 ANSWER 12 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1993-13226 DRUGU T E

TITLE: Beneficial Effects of Atrial **Natriuretic** Peptide on Exercise-Induced **Myocardial Ischemia** in Patients With Stable Effort Angina Pectoris.
AUTHOR: Lai C P; Egashira K; Tashiro H; Narabayashi H; Koyanagi S; Imaizumi T
LOCATION: Fukuoka, Japan
SOURCE: Circulation (87, No. 1, 144-51, 1993) 2 Fig. 4 Tab. 28 Ref.
CODEN: CIRCAZ ISSN: 0009-7322
AVAIL. OF DOC.: The Research Institute of Angiocardiology and Cardiovascular Clinic, Faculty of Medicine, Kyusgu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 712, Japan.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AB I.v. infusion of 28-amino aid alpha-human atrial **natriuretic** peptide (ANP, Suntory) attenuated exercise-induced **myocardial ischemia** assessed by ECG and 201T1-single photon emission CT (SPECT) in 14 patients with stable angina pectoris in a randomized, double-blind, crossover, placebo-controlled study. All patients were on nitrates and/or calcium antagonists. ANP reduced systolic B.P. at rest but not during peak exercise. Plasma cGNP rose during ANP infusion. The degree of coronary artery stenosis was assessed after intracoronary isosorbide dinitrate. ANP attenuates exercise-induced **myocardial ischemia** in patients with stable angina pectoris, possibly by improving perfusion in the ischemic zone.

L72 ANSWER 13 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1992-30261 DRUGU P E
TITLE: Effect of Neutral Endopeptidase Inhibitor in Rats with Congestive Heart Failure.
AUTHOR: Murohara Y; Johnston C I
LOCATION: Melbourne, Australia
SOURCE: Clin.Exp.Pharmacol.Physiol. (19, No. 5, 380-83, 1992) 1 Tab. 12 Ref.
CODEN: CEXPB9 ISSN: 0305-1870
AVAIL. OF DOC.: University of Melbourne, Department of Medicine, Austin Hospital, Studley Road, Heidelberg, Victoria 3084, Australia.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB I.v. SCH-39370 (Schering-Plough) decreased LV systolic pressure and LVEDP in rats with CHF produced by coronary ligation. Cardiac function was improved by increasing cardiac index and decreasing total peripheral resistance index. SCH-39370 induced a transient diuresis and natriuresis. The effects of SCH-39370 were associated with increases in urinary atrial **natriuretic** peptide (ANP) and cGMP secretion. There was no increase in plasma ANP levels. SCH-39370 did not affect HR. Neutral endopeptidase inhibition may be a new therapeutic method for treating CHF possibly by potentiating the biological activities of endogenous ANP. (congress).

L72 ANSWER 14 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1993-16375 DRUGU T E
TITLE: Acute Effects of Glyceryl Trinitrate (GTN) on Plasma Cyclic Guanosine Monophosphate (cGMP) and Atrial **Natriuretic** Peptide (ANP) in Man.
AUTHOR: Stafford I; Zhang C L; Zhang Y; Horowitz J D
LOCATION: Adelaide, Australia
SOURCE: Clin.Exp.Pharmacol.Physiol. (Suppl. 21, 67, 1992) 1 Tab.
CODEN: CEXPB9 ISSN: 0305-1870
AVAIL. OF DOC.: Cardiology Unit, The Queen Elizabeth Hospital, SA 5011,

Australia.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The acute effects of i.v. infused glyceryl trinitrate (GTN) on plasma cGMP and atrial **natriuretic** peptide (ANP) were investigated in 7 patients with **ischemic heart** disease. Acute i.v. infusion of GTN atrates associated with minimal hemodynamic effects, increased the cGMP concentration gradient across the femoral vascular bed, without marked changes in either pulmonary cGMP production or ANP secretion in either vascular bed. This may be useful as a biochemical marker in nitrate efficacy in man. (congress abstract).

L72 ANSWER 15 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1993-05030 DRUGU P
TITLE: Beneficial Effects of Trandolapril on Experimentally Induced Congestive Heart Failure in Rats.
AUTHOR: Fornes P; Richer C; Pussard E; Heudes D; Domergue V; Guidicelli J F
LOCATION: Paris, France
SOURCE: Am.J.Cardiol. (70, No. 12, 43D-51D, 1992) 8 Fig. 16 Ref.
CODEN: AJCDAG ISSN: 0002-9149
AVAIL. OF DOC.: Departement de Pharmacologie, Faculte de Medecine Paris-Sud, 63, Rue Gabriel Peri, 94276, Le Kremlin-Bicetre Cedex, France.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Long-term post-MI p.o. trandolapril (TL) in rats reduced pre- and afterload, increased cardiac index, decreased plasma ANF, and produced a delayed reversal of MI-induced cardiac morphologic alterations. Untreated rats showed an immediate fall in systolic B.P., a delayed fall in LV dP/dt and a rise in end-diastolic pressure after **infarction**, and these changes persisted thereafter. **Cardiac** index (CI) was only initially and transiently decreased. LV dilation, myocardial hypertrophy and fibrosis occurred soon after MI and worsened thereafter. Plasma ANF and urinary cGMP also increased in untreated MI rats. Thus, TL increases survival rates initially by its hemodynamic effects and in the long term by hemodynamic and cardiac morphologic effects. (congress).

L72 ANSWER 16 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1993-11371 DRUGU P T
TITLE: Cyclic GMP in Platelets - A Useful Indicator of the Effects of Nitroglycerin and Nitrate Tolerance.
AUTHOR: Watanabe H; Kakihana M; Ohtsuka S; Enomoto T; Yasui K; Sugishita Y
LOCATION: Ibaraki, Japan
SOURCE: Circulation (86, No. 4, Suppl., I715, 1992)
CODEN: CIRCAZ ISSN: 0009-7322
AVAIL. OF DOC.: University of Tsukuba, Ibaraki, Japan.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The intracellular production of cyclic GMP (cGMP) in platelets by intracoronary nitroglycerol (NTG) was investigated and the clinical value of cGMP in platelets evaluated in 10 patients with **ischemic heart** disease who had previously received nitrates (nitrates group) and 10 who had not received any nitrates (no-nitrates group). PRP was assayed for platelet cGMP, and PPP for plasma cGMP and plasma ANF. The results indicate that platelet cGMP is a useful indicator for in-situ

evaluation of NTG effects, and that patients who had received nitrates develop nitrate tolerance affecting intracellular production of cGMP by NTG. (congress abstract).

L72 ANSWER 17 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1992-06590 DRUGU T P
TITLE: Clinical Aspects of Nitrate Tolerance.
AUTHOR: Abrams J
LOCATION: Albuquerque, New Mexico, United States
SOURCE: Eur.Heart J. (12, Suppl. E, 42-52, 1991) 5 Fig. 4 Tab. 85 Ref.
CODEN: EHJODF ISSN: 0195-668X
AVAIL. OF DOC.: University of New Mexico School of Medicine, Dept. of Medicine/Cardiology, Albuquerque, NM 87131, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Nitrate tolerance (NT) is reviewed. The relationship between NT in patients and NT withdrawal from munitions workers is discussed. Mechanisms of NT discussed include -SH depletion, desensitization of the guanylate cycle, counter-regulatory neurohormonal activation and plasma volume shift. The importance of NT to the use of nitroglycerin (NTG), isosorbide dinitrate (ISDN) and isosorbide-5-mononitrate (5-ISMN) in angina pectoris, acute MI, CHF and B.P. control is discussed. Management of NT with intermittent therapy, thiol donors (N-acetylcysteine (NAC) or methionine), beta-blockers, Ca channel antagonists, ACE inhibitors (captopril and enalapril), and/or diuretics and with hydralazine is considered. Mannitol hexanitrate, molsidomine, nitroprusside, NO2/EDRF and atrial **natriuretic** factor are also mentioned. (congress).

L72 ANSWER 18 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1990-13296 DRUGU P T E
TITLE: Effects of Atrial **Natriuretic** Peptide on the Coronary Arterial Vasculature in Humans.
AUTHOR: Chu A; Morris K G; Kuehl W D; Cusma J; Navetta F; Cobb F R
LOCATION: Durham, North Carolina, United States
SOURCE: Circulation (80, No. 6, 1627-35, 1989) 5 Fig. 1 Tab. 36 Ref.
CODEN: CIRCAZ ISSN: 0009-7322
AVAIL. OF DOC.: Division of Cardiology (111A), 508 Fulton Street, Durham, NC 27705, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Intra-cardiac (i.c.) alpha human atrial-**natriuretic**-peptide 1-28 (ANP; Peninsula) caused prolonged proximal coronary dilation, in 17 male patients undergoing routine coronary angiography, and taking diuretics, beta-blockers and/or digoxin. The effect of ANP was not augmented by nitroglycerol. ANP had no effect on coronary flow. Aortic pressure and LVEDP were slightly reduced, and HR, cardiac output (CO) and LV contractility were slightly increased, all these effects being short-lived. The time course of the coronary dilation resembled that of the increase in plasma cGMP rather than plasma ANP. It is concluded that ANP warrants further study as a potential treatment for **myocardial ischemia**.

L72 ANSWER 19 OF 38 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1989-50646 DRUGU P E
TITLE: Atrial **Natriuretic** Peptide Infusion in Chronic Heart Failure in the Rat.
AUTHOR: Kohzuki M; Hodsman G P; Harrison R W; Western P S; Johnston C
LOCATION: Melbourne, Australia

SOURCE: J.Cardiovasc.Pharmacol. (13, Suppl. 6, S43-S46, 1989) 2 Tab. 20 Ref.
CODEN: JCPCDT ISSN: 0160-2446
AVAIL. OF DOC.: University of Melbourne, Department of Medicine, Austin Hospital, Heidelberg, Victoria, 3084, Australia.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB In anesthetized rats with chronic heart failure induced by coronary artery ligation, rat (1-28)-atrial **natriuretic** peptide (ANP, Peninsula) infusion induced natriuresis, diuresis and a fall in B.P., but to a lesser extent than in sham operated controls. Urinary cGMP excretion was higher in rats with MI, but rose to a level similar to controls after ANP infusion. Reduced ANP responsiveness may result from impaired postreceptor mechanisms or from physiological antagonism by angiotensin II. Reduced ANP responsiveness may partly explain impaired salt excretion during heart failure. (congress).

L72 ANSWER 20 OF 38 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5
ACCESSION NUMBER: 1994:531369 CAPLUS
DOCUMENT NUMBER: 121:131369
TITLE: Role of endogenous atrial **natriuretic** peptide on systemic and renal hemodynamics in heart failure rats
AUTHOR(S): Nishikimi, Toshio; Miura, Katsuyuki; Minamino, Naoto; Takeuchi, Kazuhide; Takeda, Tadanao
CORPORATE SOURCE: Med. Sch., Osaka City Univ., Osaka, 545, Japan
SOURCE: Am. J. Physiol. (1994), 267(1, Pt. 2), H182-H186
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To investigate the role of endogenous atrial natriuretic peptide (ANP) in rats with heart failure (HF), the authors administered HS-142-1 (HS; 3 mg/kg body wt. i.v.), a novel nonpeptide ANP-receptor antagonist, to rats with surgically induced myocardial infarction and sham-operated rats. HF was characterized by a higher left ventricular end-diastolic pressure and higher plasma ANP concn. vs. controls. HS administration significantly reduced the plasma and urinary levels of cGMP in rats with HF (plasma concn. 10.6 vs. 2.7 nM; urinary excretion 48 vs. 12 pmol/min). Systemic and renal hemodynamics were unaffected by HS administration. Urine flow (-35%) and urinary sodium excretion (-50%) were significantly decreased after HS only in those rats with HF that had no changes in systemic and renal hemodynamics. These results suggest that the elevated ANP levels in HF do not contribute directly to the maintenance of systemic hemodynamics but rather compensate for the HF mainly via diuresis and natriuresis, achieved by the inhibition of renal tubular resorption rather than by renal vasodilatation.
IT **7665-99-8, CGMP**
RL: BIOL (Biological study)
(of blood plasma and urine, in heart failure, atrial **natriuretic** factor effect on)

L72 ANSWER 21 OF 38 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:731368 CAPLUS
DOCUMENT NUMBER: 135:267247
TITLE: **Natriuretic** peptide receptor-acting substance for the treatment or prophylaxis of ischemic heart disease
INVENTOR(S): Kitakaze, Masafumi
PATENT ASSIGNEE(S): Japan
SOURCE: U.S. Pat. Appl. Publ., 9 pp.
CODEN: USXXCO

Searched by Barb O'Bryen, STIC 308-4291

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001027181	A1	20011004	US 2001-752724	20010103
JP 2001288112	A2	20011016	JP 2000-98134	20000331

PRIORITY APPLN. INFO.: JP 2000-98134 A 20000331

AB A pharmaceutical compn. and a method are provided for reducing an infarct region resulting from the ischemic necrosis of cells, esp., a pharmaceutical compn. and a method for suppressing ischemia-reperfusion injury in the treatment of ischemic heart disease. The pharmaceutical compn. and the method use a substance, as an active ingredient, which can increase intracellular cGMP prodn. by acting on a natriuretic peptide receptor, and which has the effect of reducing an infarct region. The substance is preferably a natriuretic peptide. The invention is particularly useful for the treatment or prophylaxis of ischemic disease.

IT **7665-99-8, cyclic GMP**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**natriuretic** peptide receptor-acting substance for treatment or prophylaxis of ischemic heart disease)

L72 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:588691 CAPLUS
DOCUMENT NUMBER: 133:291508
TITLE: Atrial **natriuretic** peptide reduces expression of TNF-.alpha. mRNA during reperfusion of the rat liver upon decreased activation of NF-.kappa.B and AP-1
AUTHOR(S): Kiemer, Alexandra K.; Vollmar, Angelika M.; Bilzer, Manfred; Gerwig, Tobias; Gerbes, Alexander L.
CORPORATE SOURCE: Department of Medicine II, Klinikum Grosshadern, Institute of Pharmacy, Pharmaceutical Biology, Center for Drug Research, University of Munich, Munich, 81377, Germany
SOURCE: Journal of Hepatology (2000), 33(2), 236-246
CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background/Aims: The cardiovascular hormone atrial natriuretic peptide (ANP) attenuates activation of the pro-inflammatory transcription factor NF-.kappa.B in macrophages. ANP was also shown to protect from ischemia-reperfusion injury of the rat liver. This study aimed to investigate the effects of this immunomodulatory hormone and its second messenger cGMP on the activation of the two redox-sensitive transcription factors AP-1 and NF-.kappa.B and the expression of corresponding pro-inflammatory target genes during ischemia and reperfusion of the liver. The identification of the mechanisms underlying the protection by ANP should reveal new aspects concerning the pathomechanisms of ischemia/reperfusion injury. Methods: Rat livers were perfused with and without ANP or 8-Br-cGMP preceding 24 h of cold storage in University of Wisconsin soln. During reperfusion NF-.kappa.B and AP-1 DNA binding activities were detd. in freeze-clamped liver samples by electrophoretic mobility shift assay. Protein levels of p50, p65, and of I.kappa.B were detd. by Western blot. The mRNA coding for inducible nitric oxide synthase, cyclooxygenase-2, and TNF-.alpha. was detd. by RT-PCR and Northern blot. Results: After 45 min of reperfusion DNA binding activities of NF-.kappa.B were increased, whereas in ANP pretreated livers this effect was markedly reduced. AP-1, another important redox-sensitive

transcription factor, was activated and in the course of reperfusion the subunit compn. of AP-1 changed as assessed by supershift assays. ANP markedly reduced binding activities of both forms of AP-1. 8-Br-cGMP mimicked the effects of ANP on NF-.kappa.B and AP-1. Neither inducible nitric oxide synthase nor cyclooxygenase-2 mRNA could detected. In contrast, a profound expression of transcripts coding for TNF-.alpha. was detected in the course of reperfusion and ANP markedly reduced TNF-.alpha. mRNA expression. Conclusion: ANP seems to mediate its protective effect during ischemia and reperfusion by reducing the activation of NF-.kappa.B and AP-1 via cGMP. The reduced binding activity of these redox-sensitive transcription factors was accompanied by a diminished mRNA expression of TNF-.alpha., a cytokine known to be involved in cellular damage in ischemia reperfusion injury.

IT **7665-99-8, CGMP**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(atrial **natriuretic** peptide reduces expression of TNF-.alpha. mRNA during reperfusion of the rat liver upon decreased activation of NF-.kappa.B and AP-1)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:458680 CAPLUS
DOCUMENT NUMBER: 133:145392
TITLE: .alpha.-Human atrial **natriuretic** peptide, carperitide, reduces infarct size but not arrhythmias after coronary occlusion/reperfusion in dogs
AUTHOR(S): Takagi, Gen; Kiuchi, Kaname; Endo, Takao; Yamamoto, Takeshi; Sato, Naoki; Nejima, Jun; Takano, Teruo
CORPORATE SOURCE: First Department of Internal Medicine, Nippon Medical School, Tokyo, 113-8603, Japan
SOURCE: Journal of Cardiovascular Pharmacology (2000), 36(1), 22-30
CODEN: JCPCDT; ISSN: 0160-2446
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Carperitide, a recombinant form of .alpha.-hANP, possesses potent diuretic, natriuretic, and vasodilatory activity, and inhibits the renin-aldosterone system and sympathetic nervous activity. However, its beneficial effects on ischemic myocardium have not been studied fully. The authors examd. carperitide's effects on infarct size, hemodynamics, and arrhythmia frequency in anesthetized dogs (n = 20) subjected to a 90-min coronary artery occlusion/6-h reperfusion protocol. I.v. infusion of carperitide (0.2 .mu.g/kg/min) commenced 15 min after occlusion and continued during occlusion/reperfusion. Ventricular fibrillation developed in two of 10 control vs. three of 10 treated dogs (p = NS). Hemodynamics, collateral blood flow to the ischemic wall measured 10 min after occlusion, and extent of area at risk were comparable for the two groups. Infarct size/area at risk was smaller in treated than in control dogs (4.5.+-.2.1% vs. 27.8.+-.7.8%, resp.; $p < 0.05$). During occlusion, carperitide tended to increase collateral blood flow (+39%) and significantly decreased left ventricular systolic pressure (-13%) and end-diastolic pressure (-40%) compared with baseline. In control dogs, collateral blood flow tended to decrease (-8.3%), whereas most hemodynamic parameters did not change significantly with respect to baseline. The no. of arrhythmias recorded during occlusion/reperfusion was similar in the two groups. I.v. administration of carperitide limited infarct size, but did not reduce incidence of ventricular arrhythmias after 90-min coronary occlusion/6-h reperfusion in anesthetized dogs. Although the beneficial effects of carperitide may be attributable to concomitant changes in hemodynamics and collateral blood flow, the precise mechanisms require

further investigation.

IT **7665-99-8, CGMP**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(carperitide, recombinant form of .alpha.-human atrial **natriuretic** peptide reduces infarct size but not arrhythmias after coronary occlusion/reperfusion in dog)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 24 OF 38 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:730020 CAPLUS
DOCUMENT NUMBER: 130:90866
TITLE: The guanylate cyclase-coupled **natriuretic** peptide receptor: a new target for prevention of cold ischemia-reperfusion damage of the rat liver
AUTHOR(S): Gerbes, Alexander L.; Vollmar, Angelika M.; Kiemer, Alexandra K.; Bilzer, Manfred
CORPORATE SOURCE: Department of Medicine II, Klinikum Grosshadern, Ludwig-Maximilians-University of Munich, Munich, 81377, Germany
SOURCE: Hepatology (Philadelphia) (1998), 28(5), 1309-1317
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of our studies was to investigate hormonal prevention of hepatic preservation damage by the atrial natriuretic peptide (ANP) and the mechanisms involved. Isolated perfusion of rat livers was performed in a nonrecirculating fashion. Twenty minutes of preischemic perfusion was performed with or without different concns. of ANP, followed by 24-h storage in cold University of Wisconsin (UW) soln. Two hundred nanomoles of ANP prevented hepatocellular damage during a 2-h reperfusion period as indicated by a marked attenuation of the sinusoidal efflux of lactate dehydrogenase (LDH) and purine nucleoside phosphorylase (PNP), and by reduced Trypan blue uptake. Furthermore, postischemic bile flow as an indicator of liver function was significantly improved by about 60% with 200 nmol/L ANP. No protection was conveyed by 20 nmol/L ANP nor by pretreatment with 200 nmol/L ANP for only 10 min. The effects of ANP seemed to be mediated by the guanylate cyclase-coupled A (GC-A) receptor and cGMP: whereas expression of both GC-A and GC-B receptors as well as of the GC-C receptor was found, cGMP did protect from ischemia-reperfusion damage, but selective ligands of the B and C receptor did not. To begin to det. the mechanisms of ANP-mediated protection, different parameters were investigated: ANP had no effect on portal pressure as an indicator of hepatic circulation, nor on intracellular energy depletion detd. by adenosine nucleotide concn. However, the marked augmentation of nuclear factor .kappa.B (NF-.kappa.B) binding activity during reperfusion was prevented in ANP-pretreated livers. In conclusion, pretreatment with ANP protects the rat liver from cold ischemia-reperfusion damage. This effect is mediated via the GC-A receptor and cGMP, and may be linked to an influence of ANP on NF-.kappa.B activation. Thus, ANP signaling via the GC-A receptor should be considered as a new pharmacol. target to prevent preservation injury of the liver.

IT **7665-99-8, CGMP**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(atrial **natriuretic** peptide prevention of cold ischemia-reperfusion damage of rat liver and mechanism therefor and GC-A receptor as signaling target therein)

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 25 OF 38 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:552777 CAPLUS
DOCUMENT NUMBER: 125:238019
TITLE: Protection of reoxygenated cardiomyocytes against osmotic fragility by nitric oxide donors
AUTHOR(S): Schlueter, K. D.; Jakob, G.; Ruiz-Meana, M.; Garcia-Dorado, D.; Piper, H. M.
CORPORATE SOURCE: Physiologisches Inst., Justus-Liebig-Univ. Giessen, Giessen, D-35392, Germany
SOURCE: Am. J. Physiol. (1996), 271(2, Pt. 2), H428-H434
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In ischemic-reperfused myocardium, myocardial cells are jeopardized not only by reoxygenation-induced hypercontracture but also by the development of transsarcolemmal osmotic gradient. Here the question of whether osmotic fragility of cardiomyocytes can be reduced by interventions during reoxygenation was addressed. Isolated ventricular cardiomyocytes (from adult rats), exposed to 120 min of hypoxia and subsequent reoxygenation, were used as model. With reoxygenation, medium osmolarity was reduced from 270 to 80 mosM. Loss of sarcolemmal integrity was characterized by enzyme loss from cells (creatine kinase and lactate dehydrogenase). Cardiomyocytes reoxygenated after 120 min of hypoxia hypercontracted, but enhanced enzyme loss was obsd. only at 80 mosM. The nitric oxide (NO) donors 3-morpholinosydnonimine (10 mM), sodium nitroprusside (10 mM), S-nitroso-N-acetyl-DL-penicillamine (100 .mu.M), and the antilipid peroxidant diphenylphenylenediamine (DPPD, 2.5 .mu.M) reduced enzyme loss with hyposmolar reoxygenation. Agents activating guanosine 3',5'-cyclic monophosphate (cGMP)-dependent pathways [atrial natriuretic peptide (1 .mu.M), urodilatin (1 .mu.M), and 8-bromo-cGMP (10 mM)], the contractile inhibitor 2,3-butanedione monoxime (10 mM), and the SIN-1 metabolite SIN-1C (10 mM) did not protect cardiomyocytes against osmotic fragility. The results show that increased osmotic fragility of increased adult rat cardiomyocytes can be prevented at the time of reoxygenation by NO donors and DPPD in a cGMP-independent way.
IT **7665-99-8, CGMP**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(in protection of reoxygenated cardiomyocytes against osmotic fragility by nitric oxide donors)

L72 ANSWER 26 OF 38 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:554629 CAPLUS
DOCUMENT NUMBER: 121:154629
TITLE: Discrepancy between plasma and lung angiotensin-converting enzyme activity in experimental congestive heart failure. A novel aspect of endothelium dysfunction
AUTHOR(S): Huang, Huaming; Arnal, Jean-Francois; Llorens-Cortes, Catherine; Challah, Mireille; Alhenc-Gelas, Francois; Corvol, Pierre; Michel, Jean-Baptiste
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, Paris, Fr.
SOURCE: Circ. Res. (1994), 75(3), 454-61
CODEN: CIRUAL; ISSN: 0009-7330
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The renin-angiotensin and cardiac natriuretic systems play an important role in the pathophysiol. of congestive heart failure (CHF). The status of the membrane-bound pulmonary and renal activities of three ectoenzymes involved in the regulation of these systems - angiotensin-converting enzyme (ACE), neutral endopeptidase (NEP), and aminopeptidase A (APA) - was investigated in Wistar rats 3 mo after induction of myocardial

infarction (MI) and in sham-operated (control) rats. Plasma renin activity and ACE activity, plasma angiotensin II (Ang II) levels, and atrial natriuretic factor levels were simultaneously detd. The lung ACE activity was decreased in MI rats compared with control rats, and this decrease depended on the severity of MI. Northern blot anal. showed that the lung ACE mRNA level in severe MI rats was half that of the control rats. Renal ACE activity of the MI rats was not affected, and neither renal or pulmonary NEP nor pulmonary APA activities were altered. Thus, lung ACE gene expression appears to be both organ- and enzyme-specifically regulated during CHF. Whereas plasma renin was increased in heart failure rats, plasma Ang II levels were not different from those of control rats. Thus, decreased lung ACE activity could possibly contribute to keeping plasma Ang II levels in the normal range. The decrease in lung ACE activity and mRNA levels, combined with increased plasma ACE activity, represents a novel aspect of endothelial dysfunction in CHF. This dissocn. between the membrane-bound endothelial enzyme and its circulating counterpart emphasizes the importance of simultaneously assessing the circulating and tissue components of the renin-angiotensin system in heart failure.

IT **7665-99-8, CGMP**
RL: BIOL (Biological study)
(urinary excretion of, heart failure effect on, ectoenzymes of lung and kidney in relation to)

L72 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:588308 CAPLUS
DOCUMENT NUMBER: 111:188308
TITLE: Atrial **natriuretic** peptide infusion in chronic heart failure in the rat
AUTHOR(S): Kohzuki, Masahiro; Hodsman, G. Peter; Harrison, Richard W.; Western, Patrick S.; Johnston, Colin I.
CORPORATE SOURCE: Dep. Med., Melbourne Univ., Heidelberg, 3084, Australia
SOURCE: J. Cardiovasc. Pharmacol. (1989), 13(Suppl. 6), S43-S46
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The natriuretic, diuretic, and hypotensive responses to infused atrial natriuretic peptide (ANP) were measured in rats 4 wk after myocardial infarction induced by coronary artery ligation. Rat [1-28]-ANP was infused i.v. in doses of 0.1, 0.3, and 1.0 .mu.g/kg/min for 30 min each under pentobarbital anesthesia. There was a marked natriuresis, diuresis, and fall in blood pressure in rats with infarction but each response was attenuated when compared with sham-operated controls. Urinary cGMP excretion in rats with infarction was higher than that of controls but rose to the same abs. level in both groups in response to ANP infusion (0.3 .mu.g/kg/min). Reduced ANP responsiveness may result from impaired postreceptor mechanism or from physiol. antagonism by angiotensin II. Reduced ANP responsiveness may partly explain impaired salt handling in heart failure.

IT **7665-99-8, CGMP**
RL: BIOL (Biological study)
(of urine, in chronic heart failure, atriopeptin effect on)

L72 ANSWER 28 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001275244 EMBASE
TITLE: Plasma A- and B-type natriuretic peptides: Physiology, methodology and clinical use.
AUTHOR: Boomsma F.; Van den Meiracker A.H.
CORPORATE SOURCE: F. Boomsma, University Hospital Dijkzigt, Internal Medicine, Dr. Molewaterplein 40, 3015 GD Rotterdam, Netherlands. boomsma@inw1.azr.nl

SOURCE: Cardiovascular Research, (15 Aug 2001) 51/3 (442-449).
Refs: 110
ISSN: 0008-6363 CODEN: CVREAU
PUBLISHER IDENT.: S 0008-6363(01)00195-X
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
028 Urology and Nephrology
037 Drug Literature Index
LANGUAGE: English

L72 ANSWER 29 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001125361 EMBASE
TITLE: Cardiac natriuretic peptides - Hope or hype?.
AUTHOR: Venugopal J.
CORPORATE SOURCE: J. Venugopal, Department of Pharmacology, National University of Ireland, Galway, Ireland. joshi@medscape.com
SOURCE: Journal of Clinical Pharmacy and Therapeutics, (2001) 26/1 (15-31).
Refs: 106
ISSN: 0269-4727 CODEN: JCPTED
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In recent years, biomedical science has witnessed the emergence of peptide biochemicals as significant topics of research. Some of these peptides are of little potential clinical use, while others, of which cardiac natriuretic peptides are an example, appear to be promising. This particular group of peptides (i.e. ANP, BNP and CNP) shows promising diagnostic as well as therapeutic potential for various pathological conditions. In the case of acute myocardial infarction, these peptides have significant diagnostic and predictive properties, more so than other biochemicals such as adrenaline, renin and aldosterone. In addition, ANP is found to have significant benefits over the classical anti-anginal drug glyceryl trinitrate. However, as is the case with other peptides, applying these benefits clinically may not be easy because of the structure of the compounds, but various strategies are now being applied to solve this problem. These include the use of non-peptide receptor ligands, inhibitors of ANP metabolism, gene therapy and so on. The development of drugs in clinical practice, which exploits the natriuretic peptides system therefore seems to be promising, and this article reviews advances in our understanding of these compounds.

L72 ANSWER 30 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999190738 EMBASE
TITLE: Prevention of Kupffer cell-induced oxidant injury in rat liver by atrial natriuretic peptide.
AUTHOR: Bilzer M.; Jaeschke H.; Vollmar A.M.; Paumgartner G.; Gerbes A.L.
CORPORATE SOURCE: M. Bilzer, Dept. of Medicine II, Klinikum Grosshadern, Univ. of Munich, 81377 Munich, Germany
SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology, (1999) 276/5 39-5 (G1137-G1144).
Refs: 46
ISSN: 0193-1857 CODEN: APGPDF
COUNTRY: United States

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The generation of reactive oxygen species (ROS) by activated Kupffer cells contributes to liver injury following liver preservation, shock, or endotoxemia. Pharmacological interventions to protect liver cells against this inflammatory response of Kupffer cells have not yet been established. Atrial natriuretic peptide (ANP) protects the liver against ischemia-reperfusion injury, suggesting a possible modulation of Kupffer cell-mediated cytotoxicity. Therefore, we investigated the mechanism of cytoprotection by ANP during Kupffer cell activation in perfused rat livers of male Sprague- Dawley rats. Activation of Kupffer cells by zymosan (150 .mu.g/ml) resulted in considerable cell damage, as assessed by the sinusoidal release of lactate dehydrogenase and purine nucleoside phosphorylase. Cell damage was almost completely prevented by superoxide dismutase (50 U/ml) and catalase (150 U/ml), indicating ROS-related liver injury. ANP (200 nM) reduced Kupffer cell-induced injury via the guanylyl cyclase-coupled A receptor (GCA receptor) and cGMP; mRNA expression of the GCA receptor was found in hepatocytes, endothelial cells, and Kupffer cells, and the cGMP analog 8- bromo-cGMP (8-BrcGMP; 50 .mu.M) was as potent as ANP in protecting from zymosan-induced cell damage. ANP and 8-BrcGMP significantly attenuated the prolonged increase of hepatic vascular resistance when Kupffer cell activation occurred. Furthermore, both compounds reduced oxidative cell damage following infusion of H2O2 (500 .mu.M). In contrast, superoxide anion formation of isolated Kupffer cells was not affected by ANP and only moderately reduced by 8-BrcGMP. In conclusion, ANP protects the liver against Kupffer cell-related oxidant stress. This hormonal protection is mediated via the GCA receptor and cGMP, suggesting that the cGMP receptor plays a critical role in controlling oxidative cell damage. Thus ANP signaling should be considered as a new pharmacological target for protecting liver cells against the inflammatory response of activated Kupffer cells without eliminating the vital host defense function of these cells.

L72 ANSWER 31 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999236267 EMBASE
TITLE: For the safe use of Viagra: What cardiologists need to know.
AUTHOR: Iwanaga S.
CORPORATE SOURCE: S. Iwanaga, Non-invasive Cardiology, Lab., Department of Laboratory Medicine, Keio University Hospital, Yokohama, Japan
SOURCE: Respiration and Circulation, (1999) 47/7 (709-714).
Refs: 4
ISSN: 0452-3458 CODEN: KOJUA
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
028 Urology and Nephrology
037 Drug Literature Index
LANGUAGE: Japanese

L72 ANSWER 32 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97241999 EMBASE
DOCUMENT NUMBER: 1997241999
TITLE: Heterogeneity in the vasorelaxing effect of nicorandil on dog epicardial coronary arteries: Comparison with other NO donors.

AUTHOR: Matsumoto T.; Takahashi M.; Omura T.; Takaoka A.; Liu Q.; Nakae I.; Kinoshita M.
CORPORATE SOURCE: Dr. T. Matsumoto, First Department of Internal Med., Shiga University of Medical Science, Seta, Otsu 520-21, Japan
SOURCE: Journal of Cardiovascular Pharmacology, (1997) 29/6 (772-779).
Refs: 38
ISSN: 0160-2446 CODEN: JCPCDT
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The relaxation responses to nicorandil, nitroglycerin (NTG), and cromakalim were compared in isolated dog large (>1.5 mm inside diameter) and small (<0.3 mm inside diameter) epicardial coronary arteries. Nicorandil and NTG produced more potent relaxing effects in large coronary arteries. In contrast, cromakalim produced greater relaxation in small arteries. No significant differences were observed in the nitric oxide (NO)-induced response after treatment with superoxide dismutase. The responses to 8- bromo-cyclic guanosine monophosphate (cGMP), SIN-1, and atrial natriuretic peptide did not differ in arteries of different sizes. Treatment with L- cysteine had no significant effect on the relaxation responses to NTG in both large and small coronary arteries. Oxyhemoglobin and glibenclamide inhibited relaxation induced by nicorandil in large and small coronary arteries. Oxyhemoglobin had a greater suppressive effect on the response to nicorandil in large coronary arteries than in small coronary arteries. Methylene blue inhibited the response to nicorandil in large coronary arteries. These findings suggest that nicorandil behaves predominantly as a nitrate in large epicardial coronary arteries rather than small epicardial arteries and that this difference between large and small coronary arteries with regard to the nitrate action of nicorandil may be the result of a pathway in which nicorandil is converted to NO.

L72 ANSWER 33 OF 38 EMBASE
ACCESSION NUMBER: 95292762 EMBASE
DOCUMENT NUMBER: 1995292762
TITLE: Role of nitric oxide in the regulation of myocardial function.
AUTHOR: Hare J.M.; Colucci W.S.
CORPORATE SOURCE: Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St,Boston, MA 02115, United States
SOURCE: Progress in Cardiovascular Diseases, (1995) 38/2 (155-166).
ISSN: 0033-0620 CODEN: PCVDAN
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 002 Physiology
005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Nitric oxide (NO), produced by either constitutive or inducible isoforms of NO synthase (cNOS or iNOS), influences myocardial inotropic and chronotropic responses. This pathway has been studied using NO donors or NOS inhibitors or by immune-mediated stimulation of iNOS. Although inhibition of constitutive NO activity in the heart does not influence indices of myocardial contractility, NO donors, in some species and preparations, may exert a negative inotropic effect as well as an enhancement of diastolic relaxation. The best documented cardiac action of

NO is inhibition of the positive inotropic and chronotropic responses to .beta.-adrenergic receptor stimulation. Basal NO production, presumable via cNOS, appears to exert a mild tonic inhibition of .beta.-adrenergic responses. On the other hand, excessive NO production mediated by iNnS may contribute to the myocardial depression and .beta.-adrenergic hyporesponsiveness associated with conditions such as sepsis, myocarditis, cardiac transplant rejection, and dilated cardiomyopathy. Muscarinic cholinergic stimulation of the heart appears to stimulate NO production that mediates, at least partially, parasympathetic slowing of heart rate and inhibition of .beta.-adrenergic contractility. NO- stimulated production of 3',5'-cyclic guanosine monophosphate via guanylyl cyclase accounts for many of the observed physiological actions of NO. 3',5'-Cyclic guanosine monophosphate inhibits the .beta.-adrenergic-stimulated increase in the slow-inward calcium current and reduces the calcium affinity of the contractile apparatus, actions that could contribute to a negative inotropic effect, an abbreviation of contraction, and an enhancement of diastolic relaxation. Biochemical, immunocytochemical, and molecular biological techniques have been used to show the presence of both cNOS and iNOS within the myocardium. cNOS is expressed in myocytes, endothelial cells, and neurons in the myocardium, and there is evidence for iNnS in myocytes, small vessel endothelium, vascular smooth muscle cells, and immune cells that infiltrate the heart. Taken together, these observations suggest that NO influences normal cardiac physiology end may play an important role in the pathophysiology of certain disease states associated with cardiac dysfunction.

L72 ANSWER 34 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93243400 EMBASE
DOCUMENT NUMBER: 1993243400
TITLE: Role of vasoactive peptides in blood pressure control.
AUTHOR: Brunner H.R.
CORPORATE SOURCE: Hypertension Division, University Hospital, CHUV,1011 Lausanne, Switzerland
SOURCE: Journal of Human Hypertension, (1993) 7/4 (375-381). ISSN: 0950-9240 CODEN: JHHYEN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L72 ANSWER 35 OF 38 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92186313 EMBASE
DOCUMENT NUMBER: 1992186313
TITLE: Priming of polymorphonuclear neutrophils by atrial natriuretic peptide in vitro.
AUTHOR: Wiedermann C.J.; Niedermuhlbichler M.; Braunsteiner H.
CORPORATE SOURCE: Department of Internal Medicine, Anichstrasse 35,A-6020 Innsbruck, Austria
SOURCE: Journal of Clinical Investigation, (1992) 89/5 (1580-1586). ISSN: 0021-9738 CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In ischemia-reflow states of coronary artery disease, the activation of PMN precedes the initiation of tissue damage. Release of atrial natriuretic peptide (ANP) from myocytes occurs within minutes after the onset of myocardial ischemia, which suggests a possible role of ANP in PMN

activation. To investigate this possibility, we tested the effects of ANP on functions of PMN in vitro. ANP is a potent signal for priming the PMN respiration burst to secrete superoxide anion. Phorbol 12-myristate 13-acetate, opsonized zymosan, or FMLP could all be used as triggering stimuli to demonstrate the priming of PMN activation by ANP. Only ANP fragments 1-28 and 7-28 enhanced respiration burst activity but identical preparations of ANP fragments 13-18 or 1-11 failed to do so. This structure-activity relationship is typical of receptors for ANP found in other tissues. In addition, ANP stimulated the release of .beta.-glucuronidase from PMN triggered by FMLP. The observed inhibition by ANP of FMLP-stimulated chemotaxis of PMN may be due to their enhanced adhesiveness. These data show that a classic cardiac hormone is involved in regulating important functional activities of PMN. These data support the possibility that ANP could act as a preinflammatory substance in ischemia- reperfusion states and myocardial necrosis.

L72 ANSWER 36 OF 38 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-638528 [73] WPIDS
DOC. NO. CPI: C2001-188843
TITLE: Composition for the treatment or prophylaxis of **ischemic heart** disease i.e. **myocardial infarction**, comprises a substance which can increase intracellular **cGMP** production by acting on a **natriuretic** peptide **receptor**.
DERWENT CLASS: B04 D16
INVENTOR(S): KITAKAZE, M
PATENT ASSIGNEE(S): (SUNR) SUNTORY LTD; (KITA-I) KITAKAZE M
COUNTRY COUNT: 2
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2001027181	A1	20011004	(200173)*		7
JP 2001288112	A	20011016	(200176)		7

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2001027181	A1	US 2001-752724	20010103
JP 2001288112	A	JP 2000-98134	20000331

PRIORITY APPLN. INFO: JP 2000-98134 20000331
AB US2001027181 A UPAB: 20011211
NOVELTY - A composition, (PC), for the treatment or prophylaxis of **ischemic heart** disease comprising a substance which can increase intracellular **cGMP** production by acting on a **natriuretic** peptide **receptor** and which has an effect of reducing an infarct region, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the treatment or prophylaxis, (T1), of **ischemic heart** disease, comprising the administration of a PC comprising an ingredient which can increase intracellular **cGMP** production by acting on a **natriuretic** peptide **receptor** and which has an effect of reducing an infarct region.

ACTIVITY - Vasotropic; cardiant.

MECHANISM OF ACTION - **Receptor** modulator. In models of **myocardial infarction** involving **ischemia** reperfusion, hANP, a **natriuretic** peptide, administration reduces the region of **myocardial infarction**. The region of **myocardial infarction** in the control group was 41+/- 3 %

of the at risk region when compared to 21+/-5 % in the group which received hANP.

USE - The composition is useful for suppressing ischemia **reperfusion injury** in the treatment of **ischemic heart** disease, preferably **myocardial infarction** (claimed).

ADVANTAGE - The treatment reduces **reperfusion injury** in a patient with ischemic disease. The **natriuretic** peptide has a diuretic action and lowers blood pressure.

Dwg.3/3

L72 ANSWER 37 OF 38 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-583481 [66] WPIDS
DOC. NO. CPI: C2001-173098
TITLE: New 2-phenyl-imidazo (5,1-f) (1,2,4) triazin-4-one derivatives, are phosphodiesterase inhibitors useful for treating cardiovascular, cerebrovascular or urogenital disorders.
DERWENT CLASS: B02
INVENTOR(S): BISCHOFF, E; DEMBOWSKY, K; ES-SAYED, M; HANING, H; LAMPE, T; NIEWOEHNER, U; PERZBORN, E; SCHLEMMER, K; SCHMIDT, G
PATENT ASSIGNEE(S): (FARB) BAYER AG
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 10010067	A1	20010906	(200166)*		153
WO 2001064677	A1	20010907	(200166)	GE	

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001040637 A 20010912 (200204)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 10010067	A1	DE 2000-10010067	20000302
WO 2001064677	A1	WO 2001-EP1871	20010220
AU 2001040637	A	AU 2001-40637	20010220

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001040637	A Based on	WO 200164677

PRIORITY APPLN. INFO: DE 2000-10010067 20000302

AB DE 10010067 A UPAB: 20020516

NOVELTY - 5-Alkyl-7-(cyclo)alkyl-2-(2-oxy-5-substituted-phenyl)-3H-imidazo (5,1-f) (1,2,4) triazin-4-ones (I) are new.

DETAILED DESCRIPTION - Imidazo-triazinones of formula (I) and their tautomers, salts, hydrates and pro-drugs are new.

R1, R3 = alkyl;

R2 = 1-12C alkyl or 3-8C cycloalkyl;

R4 = -NHSO2R5 or -N(SO2R6)SO2R7; COOH, -NH-CH(Ph)-P(O)(OR11)(OR12), 2-hydroxy-4-methyl-2-morpholinyl, oxiranyl, COR13 or OR14; NHCONR17R18; NHCOR24; 1-12C alkyl (optionally substituted (os) by 1-3 of OH, N3, Ph, NR28R29, OCOR30 or P(O)(O-alkyl)2; or by triazolyl (itself os by 1 or 2 of

halo, Ph, tetrahydrofuranyl, tetrahydropyranyl, alkoxycarbonyl, CONH2 or alkyl (os by OH, alkoxy, NR34R35 or OCOR36))); COR37; or a 5-membered heterocycle containing 1-3 of S, N and/or O as heteroatom(s) (os by 1-3 of halo, CF3, phenyl (os by one or more of halo or CF3), 3-6C cycloalkyl, pyrrolyl, 1-12C alkyl (os by CN, CF3, alkoxycarbonyl, alkoxy, NH2, Ph or nitrophenyl), NR43R44, NHCOCOR45, NHCOR46, NHCOCH2R47, COR48 or NHC(=NH)NH2);

R5 - R7 = vinyl or alkyl ((os) by 1-3 of CF3, halo, alkoxy, OC2F5, C2F5, -CH(CF3)2, N-(R8)-piperazino or morpholino; or 6-12C aryl (os by 1-3 of halo, CF3, NO2, CN, COOH, alkyl or alkoxy);

or R5 may also = quinolyl; 5- or 6-membered aromatic or saturated heterocycle containing 1-3 of S, O and N as heteroatom(s) (os by 1-3 of halo or alkyl); 6-chloro-imidazo (2,1-b) thiazol-5-yl; benzofurazan-4-yl; or NR9R10;

R8, R11, R12 = H or 1-4C alkyl;

R9, R10 = H, alkyl or Ph;

R13 = alkyl;

R14 = alkyl (os by 1-3 of OH, Ph or NR15R16);

R15, R16 = H, Ph or 1-4C alkyl (os by Ph);

R17, R18 = H, alkyl (os by 5-methyl-tetrahydrofuran-2-yl, tetrahydrofuran-3-yl or NR19R20) or 6-12C aryl (os by halo, trifluoroethyl or SCF3); or R18 may also = SO2R23 if R17 = H;

or NR17R18 = N-(R21)-piperazino, morpholino, R22-substituted pyrrolidino or R22-substituted piperidino;

R19, R20 = H, Ph or alkyl;

R21 = H or alkyl;

R22 = OH or alkyl (os by OH);

R23 = alkyl or aryl (os by halo); or morpholino or N-methyl-piperazino;

R24 = 1-(R26)-4-(R25)-piperazin-2-yl; alkyl (os by 6-12C aryl, itself os by OH or alkoxy); or alkyl (os by R27 or SO2R27);

R25, R26 = H, alkyl or alkoxycarbonyl;

R27 = morpholino, morpholinomethyl or N-methylpiperazino;

R28, R29 = H, Ph or alkyl (os by OH, alkoxy or Ph);

or R28R29 = 4-(5,6-dihydro-1,4,2-dioxazin-3-yl)-piperidino, 4-hydroxypiperidino, 4-(NR31R32)-piperidino or 4-(R33)-piperazino;

R30 = alkyl;

R31, R32 = H or alkyl;

R33 = alkyl, benzyl, alkoxycarbonyl, COOH, pyridyl, pyrimidyl or phenyl (os by alkoxy);

R34, R35 = H or alkyl;

R36 = alkyl;

R37 = CH2CN, morpholino, 4-(R36)-piperazino, morpholinomethyl, N-(R36)-piperazinomethyl. NR39R40, CH2NR39R40 or CH2P(O)(OR41)OR42;

R38 = H or alkyl;

R39, R40 = H or alkyl (os by OH);

R41, R42 = alkyl;

R43, R44 = H, benzyl, alkyl or Ph (os by halo or CF3);

R45 = alkoxy;

R46 = alkyl or Ph;

R47 = OH, alkoxy or OCOR49;

R48 = CH2CN or Ph (os by halo, CF3 or alkoxy); and

R49 = 1-4C alkyl;

alkyl moieties have 1-6C unless specified otherwise.

An INDEPENDENT CLAIM is included for the preparation of (I).

ACTIVITY - Hypotensive; antianginal; antiarrhythmic; vasotropic; cardiant; thrombolytic; anticoagulant; cerebroprotective; nootropic; neuroprotective; cytostatic; uropathic.

MECHANISM OF ACTION - Cyclic guanosine monophosphate (cGMP)-metabolizing phosphodiesterase (PDE) inhibitor.

(I) inhibit one or more of PDE I, PDE II and PDE V.

USE - The use of (I) is claimed for the treatment and/or prophylaxis of cGMP-related diseases, especially: (i) cardiovascular disorders,

specifically hypertension, neuronal hypertension, stable or unstable angina, peripheral or cardial vascular disease, arrhythmia, thromboembolic disease and ischemia, including myocardial infarction, cerebral apoplexy, transitory ischemic attacks, angina pectoris, peripheral blood flow disorders and restenosis after thrombolysis therapy, percutaneous transluminal (coronary) angioplasty or bypass operations; (ii) cerebrovascular disorders, specifically cerebral edema, cerebral apoplexy, reperfusion damage, cerebral trauma, edema, cerebral thrombosis, dementia or Alzheimer's disease; or (iii) urogenital disorders, specifically prostate hypertrophy, incontinence or especially erectile dysfunction or female sexual dysfunction.

ADVANTAGE - (I) selectively inhibit cGMP-metabolizing PDE's and also potentiate the activity of other agents (e.g. endothelium-derived relaxing factor, atrial natriuretic peptide or nitro-vasodilators) which increase cGMP levels by inhibiting PDE's.

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L72 ANSWER 38 OF 38 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1998-446949 [38] WPIDS
DOC. NO. CPI: C1998-135558
TITLE: Drug composition comprises **natriuretic** peptide(s) - for safe treatment of cardiac hypertrophy associated diseases and chronic heart failure.
DERWENT CLASS: B04
INVENTOR(S): FURUYA, M; HIDAKA, T; INOMATA, N; YAMAKI, A
PATENT ASSIGNEE(S): (SUNR) SUNTORY LTD
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9834636	A1	19980813	(199838)*	JA	35
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA CN HU JP KR US					
AU 9857803	A	19980826	(199902)		
EP 911034	A1	19990428	(199921)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 10534136	X	19990706	(199937)		
CN 1219134	A	19990609	(199941)		
HU 2000000954	A2	20001030	(200064)		
KR 2000064848	A	20001106	(200128)		
AU 738269	B	20010913	(200164)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9834636	A1	WO 1998-JP483	19980205
AU 9857803	A	AU 1998-57803	19980205
EP 911034	A1	EP 1998-901522	19980205
		WO 1998-JP483	19980205
JP 10534136	X	JP 1998-534136	19980205
		WO 1998-JP483	19980205
CN 1219134	A	CN 1998-800245	19980205
HU 2000000954	A2	WO 1998-JP483	19980205
		HU 2000-954	19980205
KR 2000064848	A	WO 1998-JP483	19980205
		KR 1998-707896	19981002
AU 738269	B	AU 1998-57803	19980205

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 9857803	A	Based on	WO 9834636
EP 911034	A1	Based on	WO 9834636
JP 10534136	X	Based on	WO 9834636
HU 2000000954	A2	Based on	WO 9834636
KR 2000064848	A	Based on	WO 9834636
AU 738269	B	Previous Publ.	AU 9857803
		Based on	WO 9834636

PRIORITY APPLN. INFO: JP 1997-22594 19970205

AB WO 9834636 A UPAB: 19980923

A composition for treating cardiac diseases associated with cardiac hypertrophy comprises an active ingredient capable of binding to the peptide **receptor** of GC-A and promoting production of **cGMP**.

USE - The drug composition may be used clinically to treat cardiac diseases caused by **cardiac** hypertrophy, including chronic **heart** failure, **ischaemic cardiac** diseases (claimed) and arrhythmia.

ADVANTAGE - The active substance can bind to the **natriuretic** peptide **receptor** of GC-A and promote production of **cGMP**, effectively preventing cardiac hypertrophy and leading to improvement of the pulmonary blood circulation. The substance does not affecting haemodynamic properties, blood pressure, heart beat and urine volume. Dwg.1/3

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